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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/580,797	05/30/00	IWEN	P UNMC-IWEN

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DANN DORFMAN HERRELL & SKILLMAN
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PHILADELPHIA PA 19103-2307

EXAMINER	
GOLDBERG, I	
ART UNIT	PAPER NUMBER
1655	13

DATE MAILED: 10/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/580,797	Applicant(s) IWEN ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 10, 2001.

2. Currently, claims 2-5, 19 are pending.

Election/Restrictions

3. Applicant's election with traverse of Group II in Paper No. 12 is acknowledged. Applicant has argued the restriction requirement, however, applicant has also cancelled the non-elected claims. Thus, the arguments are moot.

Applicant's have stated that it is their understanding that if methods for identifying *Aspergillus* are found allowable, claims to methods for identifying the unelected fungal species will then be searched by the examiner for inclusion in the instant application. The examiner however, points out that a Restriction was provided on page 3 for Group II. This was not an election of species. The examiner stated that the method of detecting whether *Aspergillus* is present is distinct from whether any of the other fungal species are present. The examiner also points out that the search is not coextensive. Thus a restriction is proper.

Prior to allowance, applicant is required to cancel non-elected subject matter for the claims.

Specification

4. The abstract of the disclosure is objected to because the abstract is not reflective of the elected claimed invention. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2-5 are indefinite over the recitation "known" because it is unclear what is meant by known. Known at the time the invention was made, at the time the patent publishes or rather known whenever the reader reads the publication.

B) Claim 2 appears to contain a typographical error in step b. The claim recites "oligonucleocide". It appears as though this may have been intended to recite "oligonucleotide".

C) Claims 2-5 are indefinite because it is unclear the metes and bounds of "being (SEQ ID NO: 1)". It is unclear whether the language "being" is open or closed language. Being is not a well recognized term used. Applicant is requested to clarify such that the metes and bounds are clear.

D) Claims 2-5 are further indefinite over the recitation "using one or more detestably labeled probes directed to a portion of the hypervariable region bracketed by said primers, each said labeled probe being specific for one of the said fungal species from said group to determine whether said fungal species identified by each said labeled probe is present in said sample." Claim 4 then requires that the probe consists

of SEQ ID NO: 3-8. SEQ ID NO: 5, 6, 7, 8 are directed to *Aspergillus* species probes. While portions of these probes, namely the downstream region of 18S, ITS1, 5.8S, ITS2 and the upstream region of 28S is taught, the probes contain approximately 100 bases upstream of 18S as part of the probe which have not been taught. It is unclear whether the probes of Claim 2, step d are portions, i.e. fragments from between SEQ ID NO: 1 and 2 or whether the probes are portions comprising additional materials. The claim appears to be intending to use smaller pieces of SEQ ID NO: 3-8 to distinguish and identify the specific species. Further, in the specification, probe is defined as typically containing 15-25 or more nucleotides, although it may contain fewer (page 10). Thus, the specification does not appear to be intending that the probe is 672 base pairs in length such as SEQ ID NO: 5. Furthermore, the specification states that the primer set amplifies the ITS regions of the fungal rRNA gene followed by sequence analysis of the resulting amplicon facilitates that species specific identification of fungi. This appears to be indicating that species specific identification takes place using smaller pieces of the amplified region rather than larger regions as suggested by Claim 4 (page 35). Finally, is it unclear whether species may be differentiated using SEQ ID NO: 3-8 using these probes. The species range from 91.7% identical to 79.3% identical. Depending on the hybridization conditions, the probes may not differentiate the species. Thus, Claims 2 and 4 are unclear as to their relationship and metes and bounds.

E) Claims 3-5 are indefinite over the recitation "method of Claim 1". Claim 1 is cancelled by amendment. Claim 1 was directed to product claims. It appears as

though these claims were intended to depend upon Claim 2 which is the independent method claim. Appropriate correction is required.

F) Claim 19 is indefinite because the claim appear to be directed to five different methods. For method (a) for detection of *Aspergillus*, the preamble does not appear to meet the final process step. The preamble is directed to determining whether one or more Aspergillus is present in a sample and the final process step is directed to determining which species is responsible for infection in a patient. Thus, it is unclear whether the claim is directed to detecting or whether the claim is directed to determining which species is responsible for infection. Furthermore, it is unclear how this method "uses nucleic acids having the sequence of SEQ ID NO: 3-8". The method appears to be also missing important steps. It is unclear how one may determine which species is responsible for the infection merely by comparing non-pathogenic species or pathogenic species to the sample. If non-pathogenic species is detected, there would be no indication of what species is responsible for the infection. Thus, the metes and bounds are unclear.

Claim 19b similarly appears to be directed to determining whether the species is pathogenic as opposed to detecting whether Aspergillus is present. The method steps are not in a positive active form as required by the MPEP. Furthermore, it is unclear how the method "uses nucleic acids having the sequence of SEQ ID NO: 3-8".

Claim 19c does not contain a final process step. The claim also does not have clear method steps.

Claim 19d does not contain a final process step. The claim further does not contain any method steps.

Claim 19e does not contain a final process step. Further, the claim does not contain any active method steps. "Using" is not a active process step in the sense of this claim.

Claim 19 is indefinite because the claims do not recite the basic steps of the claimed invention in a positive, active fashion (see Ex parte Erlich 3 USPQ2d, 1011). The claims describe a set of probes that might be used in a hybridization assay, but the claims fail to recite any actual steps that define the method. The limitation that the procedure "comprise the use of nucleic acids having the sequence of SEQ ID NO: 3-8" is not considered to meet the requirement of a positive process step because no guidance is given as to how to employ the oligonucleotide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2-4, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, page 315-322, 1990) and Beck (US Pat. 5,827,695, October 1998) in view of Borsuk et al. (Acta Biochimica Polionica, Vol 41, No. 1, page 73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. Vol 44, Page 225-230, pages 225-230, 1998) and Pazoutova (Genbank Accession Number AJ001331, August 1997) and Peterson (Genbank Accession Number U65306, January 1998) and Aguirre et al. (Genbank Accession Number U93683, May 1997).

It is noted that SEQ ID NO: 1 of the instant invention is identical to the ITS5 primer of White. Additionally, SEQ ID NO: 2 of the instant invention is 13 nucleotides upstream, within the 28S conserved region, of the ITS4 primer of White.

White teaches the structure of the fungal nucleic acid (Figure 1). It is noted that White teaches ITS1 and ITS5 are located in the small rDNA, and ITS4 is located in the large rDNA which would allow amplification of both the ITS1 and ITS2 reigns which are highly variable among species. Table 1 provides the nucleic acid sequence of these probes. White specifically states that ITS primers make use of conserved regions of the 18S and 28S rRNA genes to amplify the noncoding regions between them (pg 320).

Beck teaches that the state of the art with respect to obtaining ITS regions of fungal species is high and aligning the sequences to design primers which are either generic to all fungal species or alternatively species specific is routine. Beck teaches that fungal rRNA genes are organized in units, each of which encodes three mature subunits of 18S, 5.8S and 28S. These subunits are separated by two internal transcribed regions, ITS1 and ITS2. The ITS sequences are particularly suitable for the detection of specific pathoytpes of different fungal pathogens. Beck teaches that methods to clone the ITS DNA sequences are known in the art as well as general isolation of DNA from fungal isolates (col. 5, lines 12-15). Beck teaches that ideally, primers to amplify the entire ITS region were designed according to White (1990).

Neither White nor Beck specifically teaches using a primer of the instant SEQ ID NO: 2.

However, Borsuk et al (herein referred to as Borsuk) teaches the ITS1 and ITS2 regions of three *Aspergillus* species, namely *A. awamori, A. wentii, A. nidulans*, as well as partial 18S, 5.8S and 26S rRNA. As seen in the alignment of Figure 1 and 2, the 26S region of rRNA is conserved among each of the strains.

Nikkuni et al (herein referred to as Nikkuni) teaches an alignment of the ITS region of 12 strains of Aspergillus. As seen in the alignment, the 28S region is conserved between all of the strains such that the region would be an ideal target for primers indented to amplify each of the fungal species. Nikkuni teaches that it is known "that rDNA ITS are highly divergent in *Fusarium sambucinum* and their sequencing provides good reliability in the detection of close phylogentice distance. Nikkuni

teaches that nucleic acid was isolated from the fungi material in the sample (page 226, col. 1). Nikkuni teaches that the nucleic acid was amplified using primers ITS4 and ITS5 as provided by White (1990) and sequenced. Nikkuni teaches that the Its regsions of these 12 strains were reproducibly amplified by using the primer pairs of ITS4 and ITS5 (pg 227, col. 2). Nikkuni also teaches that the sequences of ITS regions could distinguish the strains (pg 229, col. 1).

Pazoutova teaches a nucleic acid sequence from *Aspergillus terreus* which contains the 5.8S rRNA gene and ITS1 and ITS2 DNA. The nucleic acid sequence contains SEQ ID NO: 2.

Peterson teaches a nucleic acid sequence from *Aspergillus niger* which contains the ITS1, 5.8S rRNA, ITS2 and 25S rRNA partial sequence. The nucleic acid sequence contains SEQ ID NO: 2.

Aguirre et al (herein referred to as Aguirre) teaches a nucleic acid sequence from *Aspergillus fumigatus* which contains 5.8 S rRNA, the ITS2 region and 28S rRNA. The nucleic acid sequence contains SEQ ID NO: 2.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of White and Beck given the specific sequences for *Aspergillus* as taught by Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre. As stated previously, it is noted that SEQ ID NO: 1 of the instant invention is identical to the ITS5 primer of White. Additionally, SEQ ID NO: 2 of the instant invention is 13 nucleotides upstream, within the 28S conserved region, of the ITS4 primer of White. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210

(Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed methods using SEQ ID NO: 2 simply represents structural and functional homologue of the previously disclosed universal primer ITS4 as taught by White, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. SEQ ID NO: 2 of the instant invention is prima facie obvious because SEQ ID NO: 2 and the ITS4 are considered functional equivalents such that both SEQ ID NO: 2 and ITS4 are located within the conserved 28S region of the fungal pathogens. The art teaches alignments of *Aspergillus* species which clearly indicates that the region targeted by SEQ ID NO: 2 is conserved among the species. The art also provides additional *Aspergillus* species which include SEQ ID NO: 2 indicating that SEQ ID NO: 2 would be conserved among *Aspergillus* species. Further, SEQ ID NO: 2 and ITS4 would both amplify the entire ITS1 and ITS2 hypervariable region. Thus, absent unexpected results or secondary considerations, SEQ ID NO: 2 is equivalent in function to ITS4.

The specification clearly states, on page 19, that the primers of the instant invention are "modifications of the original primers as stated by Henry (J. of Clinical Microbiology, Vol 28, No. 4, page 1510-1515). Henry teaches using primers of White. The specification teaches that these modifications were made to optimize the amplification procedure. However, as noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

8. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, page 315-322, 1990) and Beck (US Pat. 5,827,695, October 1998) in view of Borsuk et al. (Acta Biochimica Polionica, Vol 41, No. 1, page 73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. Vol 44, Page 225-230, pages 225-230, 1998) and Pazoutova (Genbank Accession Number AJ001331, August 1997) and Peterson (Genbank Accession Number U65306, January 1998) and Aguirre et al. (Genbank Accession Number U93683, May 1997) as applied to Claims 2-4, 19 above, and further in view of Nelson et al (US Pat. 5,827,656, October 1998).

Neither White, Beck nor Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre teach detection of more than one probe using either different signal moieties or separation moieties.

However, Nelson teaches a method for assaying a plurality of nucleic acid analytes suspected of being in a single sample by providing a plurality of probes with different labels and a sample, hybridizing and detecting (see Claim 1 of Nelson). Nelson teaches detection of pathogens. Moreover, Nelson teaches that the present invention provides rapid assay method for the detection of the presence of more than one species of organism in a test sample (col. 5, lines 45-48). Nelson teaches that the method allows for the simultaneous detection and quantification of more than one specific nucleic acid in a sample.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of White and Beck given the specific sequences for Aspergillus as taught by Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre in view of Nelson. The ordinary artisan would have been motivated to have used multiple signal moieties or solid supports for detection of more than one analyte simultaneously for the expected benefit of saving reagents, cost and time. Nelson teaches that the present invention provides rapid assay method for the detection of the presence of more than one species of organism in a test sample.

Conclusion

9. No claims allowable over the art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
October 11, 2001

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600